TARGETED THERAPIES

Targeting inflammation with collagen-binding antibodies

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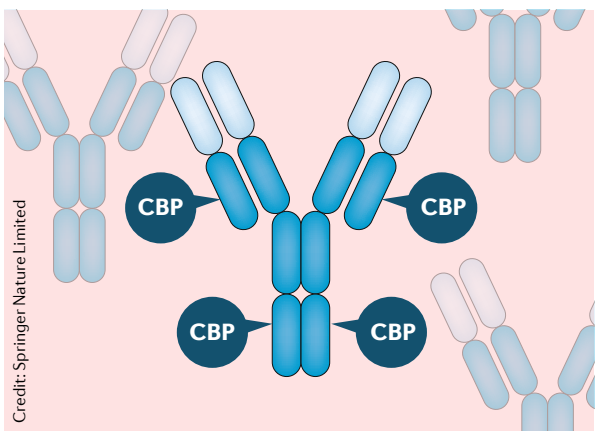
A simple translational approach to confer collagen-binding ability to therapeutic antibodies enhances their efficacy, according to the results of a new study published in *Science Advances*. Katsumata et al. demonstrated that conjugation of a collagen-binding peptide (CBP) to an anti-TNF antibody and an anti-transforming growth factor-β (TGFβ) antibody improved their anti-inflammatory effects in models of arthritis and pulmonary fibrosis, respectively.

Targeting drugs to sites of inflammation is challenging, as the dense extracellular matrix (ECM) can prevent drug penetration into a tissue, and lymphatic drainage can rapidly clear molecules from the inflamed tissue. Collagen is present in almost all tissues and is abundant around the vasculature and within inflamed tissues. Conjugation with CBP, which was derived from the ECM protein decorin, enabled systemically administered drugs to be targeted to sites of inflammation and retained there despite the ubiquitous expression of collagen. The researchers suggest that this targeting could be achieved because collagen is exposed to solutes in the bloodstream only when the vasculature is hyper-permeable, as in inflamed tissue.



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Katsumata et al. first demonstrated that CBP-conjugated anti-TNF antibody bound to types I, II and III collagen and had similar activity to the unmodified antibody in preventing binding of TNF to its receptor. The conjugated antibody also bound to collagen in tendon tissue from a patient with rheumatoid arthritis, particularly around blood vessels, and in cartilage from a patient with osteoarthritis.

In mice with collagen antibody-induced arthritis (CAIA) selectively induced in one hind paw, concentrations of the conjugated antibody were markedly higher in the inflamed paw than in the non-arthritic hind paw, and were not increased in other organs (such as the liver or kidney). The conjugated antibody also did not accumulate in the paws of healthy mice. Moreover, localization of anti-TNF antibody to the arthritic paw was substantially more pronounced following administration of the CBP-conjugated antibody than of the unmodified version.

CBP-conjugated anti-TNF antibody also suppressed the development of inflammatory arthritis more effectively than the unmodified antibody in mice with CAIA induced in all paws. Arthritis severity was attenuated in mice treated intravenously with unmodified anti-TNF antibody as compared with mice treated with control IgG, but the conjugated antibody produced an even greater reduction in disease severity. The conjugated antibody also substantially suppressed joint tissue destruction, as well as neutrophil and macrophage infiltration into the paws, unlike the unmodified antibody.

Anti-TNF antibodies are often delivered by subcutaneous injection, but as collagens are present at high concentrations in subcutaneous tissues, this route of administration could prove problematic for CBP-conjugated drugs. To address this issue, Katsumata et al. demonstrated that subcutaneously administered CBP-conjugated antibody also accumulated in the arthritic paw and was more effective against arthritis development than the unmodified antibody. The researchers suggest that the relatively moderate avidity of CBP-conjugated drugs for collagens enabled the antibody to drain from the subcutaneous tissue into the bloodstream and subsequently accumulate at inflammatory sites.

Katsumata et al. then turned to a mouse model of bleomycin-induced pulmonary fibrosis. Following intravenous administration after the onset of lung inflammation, CBP-conjugated anti-TGFβ antibody accumulated in the lungs of affected mice whereas unmodified anti-TGFβ antibody did not. The severity of lung fibrosis was attenuated in mice treated intravenously with the conjugated anti-TGFβ antibody, but not in mice treated with control IgG or the unmodified anti-TGFβ antibody.

The findings of the study suggest that engineered affinity for collagen could improve the efficacy of therapeutic antibodies in the treatment of inflammatory diseases.

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